Original Article

A comparative study of attenuation of propofol-induced pain by lignocaine, ondansetron, and ramosetron

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ABSTRACT

Background and Aims: Propofol is widely used for induction of anaesthesia, although the pain during its injection remains a concern for all anaesthesiologists. A number of techniques have been adopted to minimise propofol-induced pain. Various 5-hydroxytryptamine-3 antagonists have shown to reduce propofol-induced pain. Hence, this placebo-controlled study was conducted to compare the efficacy of ondansetron, ramosetron and lignocaine in terms of attenuation of propofol-induced pain during induction of anaesthesia. **Methods:** Hundred and fifty adult patients, aged 18–60 years, posted for various elective surgical procedures under general anaesthesia were randomly assigned to three groups of 50 each. Group R received 0.3 mg of ramosetron, Group L received 0.5 mg/kg of 2% lignocaine and Group O received 4 mg of ondansetron. After intravenous (IV) pre-treatment of study drug, manual occlusion of venous drainage was done at mid-arm with the help of an assistant for 1 min. This was followed by administration of propofol (1%) after release of venous occlusion. Pain was assessed with a four-point scale. Unpaired Student's *t*-test and Chi-square test/Fisher's exact test were used to analyse results. **Results:** The overall incidence and intensity of pain were significantly less in Groups L and R compared to Group O ($P \leq 0.001$). The incidence of mild to moderate pain in Groups O, R and L was 56%, 26% and 20%, respectively. The incidence of score '0' (no pain) was significantly higher in Group L (76%) and Group R (72%) than Group O (34%) ($P < 0.001$). **Conclusion:** Pre-treatment with IV ramosetron 0.3 mg is equally effective as 0.5 mg/kg of 2% lignocaine in preventing propofol-induced pain and both were better than ondansetron.

Key words: Lignocaine, ondansetron, pain, propofol, ramosetron

INTRODUCTION

Propofol, a widely used drug for induction, often causes local pain when administered into a peripheral vein. Many patients experience mild to moderate pain or even excruciating pain during propofol injection. Several methods have been described to reduce this pain, of which most effective and common are the use of a larger vein and mixing with lignocaine.[1-3]

Efficacy of various drugs such as lignocaine, tramadol, ketorolac and ketoprofen have been compared in reducing the propofol-induced pain.[4] Furthermore, the analgesic efficacy of drugs such as ketamine and combination of clonidine-ephedrine have been studied by various investigators.[5,6] Dexmedetomidine a newer α adrenergic agonist has been used to alleviate propofol injection pain.[7]

5-hydroxytryptamine-3 (5-HT3) antagonists such as ondansetron, granisetron, ramosetron and palonosetron have been shown to effectively alleviate propofol-induced pain individually.[8-11]

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Numerous studies have been conducted to know the better among them for prevention of post-operative nausea and vomiting (PONV)[12] but less for reducing propofol-induced pain.

Ondansetron has been proved to have a local anaesthetic effect,[13] other than antiemetic property. There is no direct evidence for the increased local anaesthetic effect of ramosetron as compared to ondansetron. However, ramosetron is benzimidazole derivative structurally independent of the previously developed 5-HT3 receptor antagonists such as ondansetron, granisetron and tropisetron. Since ramosetron is also proved to have higher efficacy than ondansetron for the prophylaxis of PONV, we assumed that it may have a similar usefulness in alleviating propofol-induced pain.

Ramosetron is one of the potent 5-HT3 antagonist commonly used as an antiemetic and has been found to be effective in prevention of early PONV compared to ondansetron.[14] With this background, we conducted a placebo-controlled study to compare the effect of ondansetron, ramosetron and lignocaine in attenuation of propofol-induced pain during induction of anaesthesia.

METHODS

We included 150 patients belonging to American Society of Anesthesiologists (ASA) physical status (PS) 1 and 2, of either sex, aged 18–60 years, weighing between 40 and 80 kg, scheduled for various elective surgical procedures under general anaesthesia. After obtaining approval from the Ethical Committee and written informed consent from the patients, the study was conducted. The exclusion criteria included patients belonging to ASA 3 and 4, patients with known cardiac disorders, other systemic disorders of lungs and liver, pregnant patients, patients for emergency procedures, those allergic to propofol and lignocaine, those with history of motion sickness, history of PONV, on nasogastric tube and patients with difficult airway.

Patients were randomly divided into one of the three groups using computer-generated random numbers (50 in each group). The drug solution was administered by an anaesthesiologist who was blinded to the constituents of the drug. Group L received 0.5 mg/kg of lignocaine and Group O received 4 mg of ondansetron and Group R received 0.3 mg of ramosetron. All the pre-treatment drugs were made into 2 ml volume with normal saline.

Prior to surgery, the patients underwent thorough pre-anaesthetic check-up and required investigations. Patients were kept fasting for 6 h for solids and were pre-medicated with oral diazepam 10 mg at night. In the operation theatre, intravenous (IV) access was established with 18-gauge cannula in suitable vein on non-dominant hand and was infused with Ringer's lactate solution. Vital signs were measured by placing an electrocardiogram, a non-invasive blood pressure monitor, end tidal carbon-dioxide and a pulse oximeter on the patients, followed by a 10 min stabilisation period. Patients were given 2 ml of pre-treatment solution IV, containing either lignocaine 0.5 mg/kg (Group L), or 4 mg of ondansetron (Group O) or 0.3 mg of ramosetron (Group R). Following 5 s of pre-treatment in all three groups, we manually occluded venous drainage at mid-arm with the help of an assistant. One minute later, the occlusion of venous drainage was released. This was followed by injection of 1% propofol (diluted in LCT, Troypofol®, Troikaa Pharmaceuticals, Ahmedabad, Gujarat, India) which was drawn immediately before use. One-fourth of the calculated dose was injected over 5 s and 15 s later the patient was assessed for pain during injection of propofol. After induction, patients were intubated and maintained with atracurium and isoflurane. At the end of surgery, residual neuromuscular blockade was antagonised with 0.05 mg/kg of neostigmine and 0.02 mg/kg of atropine. Extubation was done when the patients were fully awake and obeying commands. To evaluate the severity of propofol-induced pain, we used a four-point scale[10] with the following values: None (no discomfort at the site of injection, 0 point), mild (the presence of pain without behavioural changes, 1 point), moderate (subjective symptoms or the concurrent presence of behavioural changes, 2 points), and severe (severe pain or the concurrent presence of such responses as making a face, hunching arms or shedding tears, 3 points).

Considering previous studies, the incidence of propofol-induced pain was assumed as 80% and 50% reduction was considered significant. Based on the alpha value of 0.05 and a power value of 80%, our study required at least 41 patients per group. Assuming drop-outs, the sample size was increased to 50 per group. Continuous data are reported as mean ± standard deviation. Comparison of age, sex, weight and ASA PS between the three groups was obtained by Student's *t*-test. Categorical data are reported as numbers and percentages and are analysed using Chi-square test or Fisher's exact test

as appropriate. The value $P < 0.05$ was considered statistically significant.

RESULTS

The age, weight, gender and ASA PS of the patients are summarised in Table 1. There was no significant difference in the demographic and baseline characteristics in study groups. The incidence of pain during propofol injection in all groups is represented in Table 2.

The number of patients with no pain was significantly more in Groups L and R compared to Group O ($P \leq 0.001$). The incidence of mild to moderate pain was 28%, 13% and 11% in Groups O, R and L, respectively, and that of severe pain was 10% ($n = 5$) in Group O and 2% ($n = 1$) in both Groups R and L. The overall incidence of pain was significantly less in Groups R and L compared to Group O ($P \leq 0.001$).

DISCUSSION

IV injection of propofol causes pain at the site of injection and the pain is often reported as severe or even intolerable. The troublesome issue of pain on injection remains and has never been consistently eradicated. The exact mechanism of pain on injection is not known. The immediate vascular pain on propofol injection is attributed to a direct irritant effect of the drug[15] by stimulation of venous nociceptive receptors or free nerve endings involving myelinated Aδ fibres.[16] The delayed pain of injection has a latency of 10–20 s mediated by activation of kallikrein–kinin system.[17]

Table 1: Demographic data

Patient characteristics	Group O (*n*=50)	Group R (*n*=50)	Group L (*n*=50)
Age (years)	36.8±9.7	36.4±9.3	37.5±8.2
Sex (male/female)	21/29	21/29	22/28
Body weight (kg)	56.1±6.15	55.3±56	57.3±6.57
ASA PS 1/2	31/39	31/39	29/21

Values expressed as mean±SD. ASA PS – American Society of Anesthesiologists physical status; *n* – Number of patients; SD – Standard deviation

Table 2: Assessment of pain

Pain score	Group O *n* (%)	Group R *n* (%)	Group L *n* (%)
0	17 (34)	36 (72)*	38 (76)*
1	18 (36)	10 (20)*	09 (18)*
2	10 (20)	03 (6)	02 (4)
3	05 (10)	01 (2)	01 (2)

*$P \leq 0.001$ (highly significant). *n* – Number of patients; O – Ondansetron; R – Ramosetron; L – Lignocaine

Numerous studies have been done to investigate the most effective method and drug to reduce propofol-induced pain with variable results. There are several methods to reduce the pain caused by propofol injection including increasing the infusion rate, adding opioids, aspirin and lignocaine, cooling or diluting the propofol, and performing pre-treatment with lignocaine, ephedrine, ondansetron, metoclopramide, nafamostat mesilate, thiopentone or ketamine.[8,18] There are currently seven types of 5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, alosetron, tropisetron and ramosetron)[19] and the effect of many of these drugs has been studied in reducing propofol-induced pain. 5-HT3 receptor antagonists bind to opioid μ-receptor thus acting as agonists. In addition, 5-HT3 receptors are involved in the nociceptive pathway, and this may be the mechanism of these drugs' analgesic effect.

Local anaesthetics contain hydrophilic and hydrophobic structures separated by an intermediate amide or ester linkage. The hydrophilic group is a tertiary or secondary amine, and the hydrophobic group an aromatic moiety. Although ondansetron does not possess this aromatic moiety, it has been shown to block sodium channels.[13] Recently, ondansetron has been shown to bind to opioid μ-receptors in humans and exhibit agonist activity.[20] These properties, together with the observation that 5-HT3 receptors are involved in the nociceptive pathways, have been postulated to explain the anti-nociceptive properties of ondansetron. Despite that the 5-HT3 receptor antagonist ondansetron and ramosetron share their mechanism of action, they have different chemical structures and exhibit differences in affinity for the receptor, dose response and duration of effect.

Ramosetron is a tetrahydro-benzimidazole derivative structurally independent of previously developed drugs such as ondansetron, granisetron and tropisetron. Ramosetron is more potent and has longer lasting effects because of a slower rate of dissociation from the target receptor and higher binding affinity.[21] Since there is no data available regarding the effectiveness of ramosetron compared to ondansetron and lignocaine presently, we conducted this study to evaluate and compare the effect of all three drugs.

In a study by Ahmed *et al.*, the incidence of propofol injection pain was reduced from 60% to 15% after granisetron pre-treatment.[22] In another study, severity but not the incidence of pain on injection

was significantly reduced by dolasetron (50%) compared with placebo, and there was no significant difference between dolasetron and lignocaine.[23] The incidence of pain was reported to be 60% and 38% respectively with pre-treatment by ramosetron 0.3 mg or combination with ramosetron and lignocaine 20 mg in another study.[24] These results show effective reduction in propofol injection pain. In a study of the effect of pre treatment by palonosetron (0.075 mg) on propofol-induced pain. 72.5% of patients experienced a decrease in the occurrence of propofol-induced pain.[11]

The results of our study showed that pain caused by propofol had a significant difference between different groups. Seventeen patients (34%) in ondansetron group had no pain. In contrast, the number of patients without pain in ramosetron and lignocaine groups were 36 (72%) and 38 (76%), respectively. A systematic review of 56 studies, including 6264 patients and 12 various drugs, showed that IV lignocaine (0.5 mg/kg) can reduce the pain up to 60%.[25]

Other studies have shown largely similar results with the use of lignocaine. Lignocaine 1%, 4 ml was shown to reduce the pain of propofol injection by 68%[26] and lignocaine 50 mg was found to be slightly better than ondansetron 4 mg in attenuating pain associated with propofol injection.[27] Our studies have also revealed lignocaine to be more effective in reducing propofol-induced pain compared to ondansetron.The incidence of pain was 65% in the placebo group and in lignocaine (40 mg) and ramosetron (0.3 mg) pre-treated groups, it was 35% and 30%, respectively in another study. There is a significant decrease in moderate and severe pain (5% in each) compared with normal saline group (25% and 30%, respectively).[10] In our study, the incidence of pain in ramosetron and lignocaine group were 28% and 24%, respectively. Furthermore, the incidence of moderate to severe pain in ramosetron and lignocaine group were 8% and 6%, respectively, in our study. These results show that there is a significant reduction in the pain for propofol injection and both lignocaine and ramosetron are equally effective.

The results of a study done by Alipour *et al*.[28] showed that pain caused by propofol had a significant difference between different groups. The number of patients without pain was 39 in lignocaine and granisetron group (69.64%), 29 in magnesium sulphate group (51.78%), 22 in ondansetron group (39.28%) and 16 in paracetamol group (28.57%), ($P \leq 0.001$). They concluded that propofol injection pain was less in lignocaine and granisetron groups, in comparison with the others ($P \leq 0.001$). Similarly, in our study, the number of patients without pain were 17 (34%) in ondansetron group, 36 (72%) and 38 (76%) in ramosetron and lignocaine groups, respectively. The effects of lignocaine and ramosetron are similar and higher than the ondansetron group.

In the current study, pre-treatment with ramosetron was as effective as lignocaine and more effective than ondansetron in reducing the occurrence of propofol-induced pain. Of various types of 5-HT3 receptor antagonists, ramosetron is uniquely effective in the management of early PONV. A study done by Swarika *et al*. reported that ramosetron 0.3 mg IV was more effective than palonosetron 0.075 mg and ondansetron 8 mg in the early post-operative period.[12] Similarly, another study reported that ramosetron 0.3 mg and ondansetron 8 mg were more effective than ondansetron 4 mg for the prevention of PONV (2 h). Thus, pre-treatment with ramosetron is an effective method of reducing the occurrence of propofol-induced pain and has the advantage of preventing PONV without the additional administration of other drugs.[29]

Considering that there was no difference in the outcome of propofol-induced pain with either of the drugs, the use of ramosetron would only add to the cost of treatment. The choice of agent should, therefore, be individualised with due consideration to the cost-effectiveness and benefit to the patient.

CONCLUSION

Pre-treatment with IV ramosetron 0.3 mg and lignocaine 0.5 mg/kg significantly reduced the propofol-induced pain when compared to ondansetron 4 mg. Therefore, ramosetron alone can be used to reduce the both propofol-induced pain and PONV.

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Conflicts of interest

There are no conflicts of interest.

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